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cont a control sample of cells is indicative of said substance inhibiting Alk-1 phosphorylation of Smad1 or Smad5.

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### REMARKS

Further to discussions with Examiners Kunz and Romeo on November 16, 2001 and discussions with Examiner Romeo on December 10, 2001, applicants have canceled claims 1-28 without prejudice and expressly reserving the right to pursue the subject matter of the canceled claims in one or more subsequently filed applications and submit replacement claims 29-53.

Claims 29-53 relate to a method for determining if a substance inhibits binding of TGF- $\beta$  to Alk-1 comprising contacting a cell that expresses an Alk-1 with said substance in the presence of TGF- $\beta$  and determining if the substance inhibits binding of TGF- $\beta$  to Alk-1, and to a method for determining if a substance inhibits Alk-1 activation by contacting a first sample of cells that express a constitutive Alk1 and express Smad1 or Smad5 with the substance and determining if Smad1 or Smad5 phosphorylation is inhibited. Support for these claims is found throughout the specification<sup>1</sup>, e.g., on page 38, lines 31-34 wherein applicants disclose inhibiting the Alk-1 and TGF- $\beta$  interaction with, e.g., antibodies to the extracellular domain of ALK-1, or to TGF- $\beta$ . Support is also found on page 35, lines 16-32 wherein applicants demonstrate Alk-1 binds to TGF- $\beta$ . Further support is found on page 35, line 33 to page 36, line 21, wherein applicants disclose that activation of Alk-1 by TGF- $\beta$  leads to phosphorylation of Smad-1 or Smad-5. Additional support for the added claims is found on page 37, lines 26 to 32, wherein applicants disclose:

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<sup>1</sup> For example, support for claim 33 is found on page 35; support for claim 34 on page 36 lines 1-3; Support for claims 36-37 is found on page 35 lines 1-12; support for claim 35 on page 36, line 35 to page 37, line 8; support for claims 38-42 is found on page 35, line 33 to page 36 line 1;

"TGF- $\beta$ , as has been shown, does bind to Alk-1, leading to phosphorylation of Smad-1. Hence, by determining a value for TGF- $\beta$  alone, one can then compare a value determined with amounts of the substance to be tested, in the presence of TGF- $\beta$ . Changes in the phosphorylation levels can thus be attributed to the test substance."

Support is also found on page 37, lines 15-19 wherein applicants state:

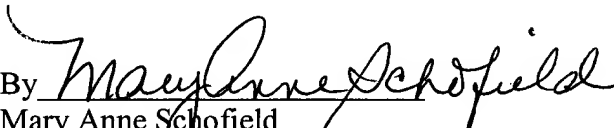
"...as ALK-1 has been identified as a key constituent of the pathway by which Smad-1 is phosphorylated, one can contact cells which express both Smad-1 and Alk-1 with a substance of interest and then determine if the Smad-1 becomes phosphorylated."

The foregoing demonstrates the claims are supported by the application and applicants respectfully request entry of this supplemental amendment.

Commissioner is hereby authorized to charge any deficiencies to Deposit Account No. 06-2375.

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Respectfully submitted,

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support on page 37, lines 15-17 and lines 21-33; support for claim 46 is found on page 35, and; support for claim 47 is found on page 35, line 33 to page 36 line 1.